analyte with a coupled oligonucleotide which interacts with the first proximity probe.

Please add new claim 25:

25. (New) A method for detecting one or more analytes in solution, comprising:

a) binding of two or more proximity probes to a respective binding site on said one or more analytes not immobilized on a solid support, wherein the proximity probes are comprised of a binding moiety and nucleic acids coupled thereto;

b) allowing the binding moiety to bind to the one or more analytes other than by Watson-Crick base pairing and allowing the nucleic acids to interact with each other if they are in close proximity to each other; and

c) detecting the degree of interaction between the nucleic acids.

REMARKS

The Official Action of September 12, 2002, and the prior art cited and relied upon therein have been carefully reviewed. The claims in the application are now claims 1-7, 13-15, and 17-25, and these claims define patentable subject matter warranting their allowance. No claims have been allowed. Favorable reconsideration and such allowance are respectfully urged.

Briefly, this invention relates to sensitive rapid and convenient assays for detection and quantification of one or several analytes in solution using proximity probes. This method depends on the simultaneous and proximate recognition of target molecules by pairs of affinity probes, which results in a detection signal capable of amplification.

Claim 14 is rejected under 35 USC 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. This rejection is respectfully traversed. The claim has been amended in accordance with the Examiner's helpful suggestion. Withdrawal of the rejection is therefore respectfully requested.

Claim 4 is rejected under 35 USC 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. This rejection is respectfully traversed. This claim has been amended so that a Markush group lists the possible analyte or analytes. Withdrawal of the rejection is therefore respectfully requested.

Claims 1-7 and 13-15 remain rejected under 35 USC 102(b) as being anticipated by Landegren WO 97/00446. This rejection is respectfully traversed.

Claim 1 has been amended to explicitly recite that the one or more analytes remain free in solution throughout the assay and are not immobilized on a solid support, as opposed to the method of the cited reference. Further, the closed "consisting of" language has been employed. Another point of distinction is that in the prior art patent, the "proximity probes" are united, whereas in the present invention the probes are clearly recited as being two or more separate units. There is therefore no anticipation of applicants' claims.

Withdrawal of the rejection is therefore respectfully requested.

Claims 1, 3-5, 7, 14 and 17-18 remain rejected under 35 USC 102(b) as being anticipated by Landegren et al (U.S. Patent No. 4,988,617). This rejection is respectfully traversed.

As noted above, Claim 1 has been amended to explicitly recite the feature of non-immobilization and the closed "consisting of" language has been employed. Again in this prior art patent, the "proximity probes" are united, unlike in the instant invention. Claim 1 makes clear that the probes are two or more separate units.

Therefore, withdrawal of the rejection is in order and is respectfully requested.

Claims 1-3, 5, 7, 14 and 16 stand rejected under 35 USC 102(b) as being anticipated by Landegren et al (U.S. Patent No. 5,871,921). This rejection is respectfully traversed.

As noted above, Claim 1 has been amended to employ closed "consisting of" language. Once more with this prior art reference, the probes are a unit and in the present invention the probes are clearly recited as being two or more separate units. As there is no anticipation, reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-8, 13 and 17-24 are rejected under 35 USC 103a as being unpatentable over Landegren and in view of Royer et al. This rejection is respectfully traversed.

The Landegren reference is directed to an immunoassay requiring an immobilized reagent, which has affinity for a specific macromolecule, further comprising a second and third affinity reagent that are modified with crosslinkable compounds. This arrangement enables conjugation of the second and third affinity reagents only when both are bound to the macromolecule of interest and amplification of a resulting signal. Royer teaches methods, apparatus and compositions for ligating ligands binding to a common receptor. Of particular emphasis are polynucleotide probes

having photoreactive functional groups. These probes assume positions on a target polynucleotide wherein the photoreactive groups are in juxtaposition. Activation of the photoreactive functional groups with radiant energy then forms a probe reaction product in which the probes are bound to each other. It is suggested that support is required in order for these reactions to occur. E.g., "A preferred method for assaying a sample for a target polynucleotide includes contacting a sample under binding conditions with a first probe, a second probe, and a support." (Col. 6, lines 13-15); "In one embodiment of the present invention, the first probe or the probe reaction product is irreversibly associated with the capture support by further photoreactive functional groups. Preferably, the support is retrievable, capable of substantially homogeneous dispersion into the medium containing the probe with the capture ligand." (Col. 6, lines 43-47), etc.

Because the Landegren reference, as discussed above, requires the immobilization of the analyte on a solid support and teaches that the probes are a unit, it does not teach the method of the instant invention. The Royer disclosure also does not teach or suggest the invention, and both teach away from the present invention because they require that a probe to be linked in an immobile fashion to a support. Therefore,

the combination of Landegren and Royer, even if obvious (which is not admitted by the Applicants) cannot render the claimed invention obvious.

New claim 25 is patentable because it recites the feature that the one or more analytes are not immobilized on a solid support, unlike the prior art. Additionally, Watson-Crick base pairing, which is used in the some of the prior art, is avoided.

The claims are now free of the prior art. Favorable consideration and allowance is earnestly solicited.

Respectfully submitted,

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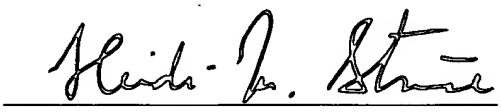
By 
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Version with Markings to Show Changes Made

1. (Thrice Amended) A method for detecting one or more analytes~~(s)~~ in solution, ~~characterised by~~consisting of the steps of:

a) binding of two or more proximity probes to a respective binding site on said one or more analytes~~(s)~~ not immobilized on a solid support , wherein the proximity probes are comprised of a binding moiety and thereto coupled nucleic acids;

b) allowing the binding moiety to bind to the one or more analytes~~(s)~~ other than by Watson-Crick base pairing, and allowing the nucleic acids to interact with each other if they are in close proximity to each other; and

c) detection of the degree of interaction between the nucleic acids ~~with the proviso that the binding moieties and the analyte(s) not all comprise nucleic acid~~.

4. (Amended) A method according to claim 1, wherein the ~~analyte(s)~~ one or more analytes are selected from the group consisting of ~~is/are~~ proteins~~(s)~~, protein aggregates~~(s)~~, prions~~(s)~~ ~~and/or~~ and nucleic acids~~(s)~~.

6. (Amended) A method according to claim 1, wherein the binding moieties are antibodies and said antibodies each bind to the one or more analytes ~~analyte(s)~~

via a further antibody having binding specificity for the one or more analytes analyte(s), and wherein the binding moieties are directed against the Fc portion of the further antibody.

14. (~~Twice~~Thrice Amended) A method according to claim 1, wherein the first proximity probe is comprised of purified analyte coupled to an oligonucleotide and the second proximity probe is comprised of a binding moiety specific for the analyte with a coupled oligonucleotide ~~capable of interacting~~ which interacts with the first proximity probe.